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A STUDY OF THE BUFFER VALUE OF THE BLOOD*

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In order that the various functions of the body may be properly performed, it is essential that the blood maintain its slightly alkaline reaction within extremely narrow limits. When this degree of alkalinity is diminished, a condition of acidosis, with its accompanying phenomena, is observed. A truly acid reaction of the blood (that is, a hydrogen-ion concentration greater than pH-7.0†) is incompatible with life.

Various protective mechanisms serve to maintain the acid-base equilibrium of the organism and thereby protect the blood from significant changes in hydrogen-ion concentration. Such processes are increased production of ammonia, the excretion of carbon dioxid by the lungs, the excretion of nonvolatile acids by the kidneys, and finally, the buffer action of the blood itself.[1]

By the term "buffer action" of a mixture is meant its ability to take up considerable amounts of acid or alkali when these are added to it, without appreciable change in hydrogen-ion concentration. The blood is such a buffer mixture, owing largely to its content of carbonates and phosphates, and, to a lesser extent, its protein.

Much valuable work has been done to determine the rôle played by each of the factors concerned in the maintenance of acid-base equilibrium, but a precise investigation[2] of the "buffer value" of the blood has not been undertaken, owing to technical difficulties. The utilization of the recently-described dialysis-indicator method[3] for determining variations in the hydrogen-ion concentration of the blood has made possible a quantitative study of its buffer value.

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* From the Medical Clinic of the Johns Hopkins Hospital.

† pH is the commonly accepted symbol for hydrogen-ion concentration.

1. For a detailed discussion of the mechanisms involved in the maintenance of acid-base equilibrium in the body, see Henderson, L. J., Ergebn. d. Physiol, 1909, viii, 254.

2. During the course of this study, a preliminary communication on "The Nature and Detection of Diabetic Acidosis," by Van Slyke, Stillman and Cullen, appeared in the Proc. Soc. Exper. Biol. and Med., 1915, xii, 165. The fact that the dialysis-indicator method was being utilized for determining the buffer value of the blood was announced with the presentation of our method before the Association of American Physicians, May, 1915. (See Tr. Assn. Am. Phys., 1915, and abstract in Jour. Am. Med. Assn., 1915, lxiv, 2162.)

3. Levy, R. L., Rowntree, L. G., and Marriott, W. McKim: A Simple Method for Determining Variations in the Hydrogen-Ion Concentration of the Blood, THE ARCHIVES INT. MED., 1915, xvi, 389.

TECHNIC

The determinations may be carried out on whole blood, serum or plasma, but it is preferable to use whole blood, since in this way conditions in the body are most closely approximated.

Two cubic centimeters of blood are placed in each of seven test tubes and allowed to stand for five or six minutes, until a thin layer of plasma at the top has been cleared of cells, hemolysis on the subsequent addition of acid and alkali thereby being prevented. The blood in the first tube is used for a determination of the pH. To each of the next three tubes is added fiftieth-normal hydrochloric acid—0.1 c.c to the first, 0.2 c.c. to the second, and 0.3 c.c to the third. Similarly, increasing amounts of fiftieth-normal sodium hydroxid solution are added to the last three tubes. The tubes are inverted once for the purpose of mixing. Each portion of blood is then separately dialyzed for six minutes against 2.5 c.c. of 0.8 per cent. salt solution and the pH of the dialysate determined by adding 5 drops of an indicator, phenolsulphonephthalein, the reading being determined by comparing with a series of standard colors.

Numerous experiments were carried out to determine the influence of various factors on the results.

1. *Effect of Temperature.*—The dialysate at temperatures ranging from 18 to 37 C. may be identical or may show slight changes,[4] but within these extremes, no essential change is seen in the buffer value of either blood or serum. The determinations can, therefore, be carried out at room temperature, without regard for the slight variations so encountered.

2. *Length of Time Elapsing Between the Withdrawal of Blood and the Carrying Out of Determinations.*—The blood may be kept for as long as twenty-four hours without change in the pH or buffer values, providing it is collected in hard glass tubes which are filled to the top, tightly stoppered, and immediately placed on ice.

3. *Length of Time the Acid or Alkali is in Contact with Blood or Serum.*—A series of experiments was carried out in which the time of contact varied from two to thirty minutes. Within these limits, identical buffer values were obtained in all cases.

4. *Loss of Carbon Dioxid.*—Obviously, the carbon dioxid tension in the blood is important. Control experiments, using the dialysis-indicator method with carbon dioxid at its normal tension, and with blood from which carbon dioxid had been shaken out, showed marked differences in pH. It is possible to collect the blood in such a way that the loss of carbon dioxid is minimal and fairly constant. This is accomplished by withdrawing blood with a syringe or pipet, filling the test tube practically to the top, promptly stoppering, avoiding unnecessary shaking, and placing immediately on ice. Duplicate determinations on the same sample, or on different specimens from the same individual, yield essentially identical results under these conditions.

4. Levy, Rowntree and Marriott, loc. cit., note 3. The time of exposure to a higher temperature is obviously a determining factor.

MODE OF EXPRESSION OF RESULTS

All results are expressed in terms of cubic centimeters of fiftieth-normal hydrochloric acid or sodium hydroxid per 2 c.c. of blood. The following terms are used:

1. *Buffer for Acid or Alkali.*—These represent the amounts of acid or alkali which can be added to blood or serum without change in the pH of the dialysate.[5] The sum of the buffer for acid and that for alkali yields the *total buffer.*

2. *Reserve Buffer for Acid or Alkali.*—These represent the amounts of acid or alkali which can be added to blood or serum without causing a change in the pH of the dialysate beyond the limits of normal.[6] The sum of the two yields the *total reserve buffer.* The reserve buffer, therefore, represents the simple buffer value *plus* the amount of acid or alkali taken care of by the blood without change in reaction beyond the limits of normal pH values. From a clinical standpoint it is the simple buffer values for acid and alkali which are of the greatest significance.

ANALYSES OF CLINICAL RESULTS

The work is based on a study of sixty-five cases, involving considerably more than 100 buffer determinations. The results may best be presented by dividing the cases into four groups.

1. *Normal Individuals (Twenty-Four Cases).*[7]—Determinations were made on both blood[8] and serum, the results appearing in Tables 1 and 2. It is noteworthy that the time elapsing between the previous meal and the withdrawal of blood for examination made no essential difference in the buffer values.

(*a*) *Blood.*—Normal blood takes 0.1 c.c. of acid or alkali without change in pH. It, therefore, has a buffer for acid and alkali of at least 0.1, though it may have a buffer of 0.2 to 0.4. The average buffer, both for acid and alkali is 0.18. The total buffer ranges from 0.2 to 0.7, with a group average of 0.36.

The reserve buffer[9] for both acid and alkali varies from 0.1 to 0.4, the group average for the acid being 0.27, that for the alkali 0.31. The total reserve buffer varies from 0.4 to 0.7, the group average being 0.58.

(*b*) *Serum.*[10]—Normal serum always takes 0.1 c.c. of acid without change in pH. It may have a buffer for acid of from 0.1 to 0.3; the

5. No attempt was made to determine changes smaller than 0.05.

6. Normal pH values are: Blood, 7.4 to 7.6; Serum, 7.6 to 7.8.

7. The blood on which these determinations were made was obtained from patients in the Genito-Urinary Dispensary, a majority of whom were under treatment for local infections of the lower genito-urinary tract. No luetic individuals are included in the series.

8. The blood was collected in tubes containing just sufficient carbonate-free sodium oxalate to prevent clotting.

9. The reserve values throughout are not absolute, since in many instances 0.3 c.c of acid and alkali failed to carry the pH beyond normal limits.

10. The values for oxalated plasma are essentially the same as those for serum. Throughout the later studies only whole blood was utilized, for the following reasons: 1. In the body it is with the buffer of the blood as a whole with which we are concerned. 2. Less blood suffices. 3. Centrifugalization, together with the resultant loss of carbon dioxid, is avoided.

TABLE 1.—Normal Cases

Case No.	Blood									Serum										Time Elapsing Since Last Meal, Hours
	pH	+ N/50 HCl (c.c.)				+ N/50 NaOH (c.c.)				pH	+ N/50 HCl (c.c.)					+ N/50 NaOH (c.c.)				
		0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.4		0.1	0.2	0.3	0.4	0.05	0.1	0.2	0.3	0.4	
1	7.6	7.6	7.6	7.55	7.5	7.6	7.7	7.8	7.8	7.8	7.8	7.7	7.6	7.5	....	7.8	7.95	7.95	8.2	1¾
2	7.55	7.55	7.55	7.45	7.45	7.55	7.55	7.6	7.65	7.7	7.7	7.7	7.6	7.5	....	7.7	7.9	8.0	8.0	2
3	7.6	7.6	7.6	7.5	7.45	7.6	7.6	1.65	7.7	7.7	7.7	7.65	7.55	....	....	7.7	7.8	7.8	7.9	
4	7.5	7.5	7.5	7.35	7.3	7.5	7.55	7.6	....	7.7	7.7	7.7	7.65	7.6	....	7.7	7.8	7.95	7.95	6
5	7.55	7.55	7.55	7.45	7.45	7.55	7.55	7.65	7.7	7.7	7.7	7.65	7.6	7.55	....	7.9	7.95	8.0	8.05	2
6	7.55	7.55	7.45	7.35	7.3	7.55	7.55	7.55	7.55	7.7	7.7	7.7	7.55	7.55	....	7.8	7.9	7.95	8.0	2
7	7.45	7.45	7.45	7.45	7.3	7.45	7.45	7.55	7.55	7.7	7.7	7.65	7.6	7.5	....	7.7	7.95	8.0	8.1	1¾
8	7.55	7.45	7.45	7.35	7.3	7.55	7.6	7.6	7.6	7.7	7.7	7.6	7.5	7.45	....	7.7	7.9	7.95	8.0	4½
9	7.55	7.55	7.5	7.45	7.45	7.55	7.55	7.65	7.65	7.7	7.7	7.7	7.6	7.5	7.75	7.9	7.9	8.0	8.0	2½
10	7.45	7.45	7.45	7.3	7.25	7.45	7.55	7.55	7.55	7.7	7.7	7.55	7.5	7.45	....	7.7	7.9	7.95	8.0	2
11	7.45	7.45	7.3	7.25	7.25	7.45	7.45	7.55	7.55	7.7	7.7	7.55	7.45	7.45	....	7.7	7.9	7.9	7.9	2½
12	7.45	7.45	7.35	....	7.35	7.45	7.45	7.5	7.5	7.65	7.65	7.55	7.45	7.45	7.65	7.75	7.95	8.0	..	1¾
13	7.45	7.45	7.45	7.45	7.35	7.45	7.45	7.45	7.45	7.65	7.65	7.55	7.45	7.35	7.65	7.75	7.85	8.05	..	2
14	7.45	7.45	7.45	7.35	7.35	7.45	7.5	7.55	7.55	7.65	7.65	7.55	7.45	7.35	7.65	7.85	7.85	8.05	..	2
15	7.45	7.45	7.45	7.35	7.35	7.45	7.45	7.5	7.55	7.65	7.65	7.45	7.45	7.45	7.65	7.8	7.8	7.85	..	21
16	7.45	7.45	7.45	7.4	7.35	7.45	7.55	7.55	7.55	7.8	7.8	7.6	7.55	7.45	7.8	7.8	7.8	7.9	..	5
17	7.45	7.45	7.45	7.4	7.4	7.45	7.55	7.7	7.75	7.7	7.7	7.65	7.6	7.55	7.7	7.8	7.9	8.05	..	2
18	7.45	7.45	7.45	7.4	7.35	7.45	7.55	7.65	7.7	7.65	7.65	7.45	7.45	7.35	7.65	7.8	7.9	7.9	..	3
19	7.45	7.45	7.35	7.35	7.35	7.45	7.55	....	7.55	7.75	7.75	7.7	7.6	7.5	7.85	7.9	7.9	8.1	..	2
20	7.55	7.55	7.45	7.45	7.45	7.55	7.55	7.7	....	7.75	7.75	7.65	7.65	7.55	7.75	7.75	7.9	8.1	..	2
21	7.55	7.55	7.55	7.55	....	7.55	7.55	7.55	....	7.65	7.65	7.55	7.45	....	7.65	7.75	7.75	7.8	..	2
22	7.45	7.45	7.45	7.45	....	7.45	7.45	7.5	....	7.65	7.65	7.6	7.5	....	7.65	7.75	7.85			
23	7.45	7.45	7.45	7.45	....	7.45	....	7.55	....	7.65	7.65	7.55	7.55	....	7.65	7.65	7.75			
24	7.45	7.45	7.35	7.35	....	7.45	7.45	7.45	....	7.65	7.65	7.55	7.45	....	7.65	7.7	7.8			

average is 0.11. Its buffer for alkali is very variable; a change may be encountered on the addition of from 0.05 to 0.3 c.c. of fiftieth-normal sodium hydroxid; the average is 0.07. The total buffer for serum [illegible] from 0.1 to 0.3, the group average being 0.18.

The reserve buffer for acid varies from 0.1 to 0.4, the group average being 0.2. The reserve buffer for alkali ranges from 0 to 0.3, the group average being 0.12. The total reserve buffer varies from 0.15 to 0.6, the average being 0.33.

TABLE 2.—Summary of Twenty-Four Normal Cases

		Blood		Serum	
		Extremes	Group Average	Extremes	Group Average
Buffer	For acid	0.2 - 0.4	0.18	0.1 - 0.3	0.11
	For alkali	0.2 - 0.4	0.18	0 - 0.3	0.07
	Total	0.2 - 0.7	0.36	0.1 - 0.3	0.18
Reserve buffer	For acid	0.2 - 0.4	0.27	0.1 - 0.4	0.2
	For alkali	0.2 - 0.4	0.31	0 - 0.3	0.12
	Total	0.4 - 0.7	0.58	0.15 - 0.6	0.33

TABLE 3.—Miscellaneous Cases with Normal pH and Normal Buffer Values; Sixteen Cases; Twenty Determinations

		Blood	
		Extremes	Group Average
Buffer	For acid	0.1 - 0.3	0.13
	For alkali	0.1 - 0.3	0.17
	Total	0.2 - 0.5	0.3
Reserve buffer	For acid	0.1 - 0.3	0.25
	For alkali	0 - 0.3	0.23
	Total	0.3 - 0.6	0.48

Although the total buffer value or the total reserve value may be great, the buffer for either acid or alkali may be small; in other words, the buffer may be great for acid and small for alkali, or vice versa. This can be determined only by actual study of the individual acid and alkali buffer values, and it is obviously not shown by a figure expressing the total buffer value.

2. *Miscellaneous Cases with Normal pH and Normal Buffer Values.*—Twenty determinations were made on sixteen cases, including instances of diabetes mellitus, pernicious anemia, myeloid leukemia, typhoid fever, pregnancy, surgical cases before and after anesthesia, exophthalmic goiter and chronic nephritis (Table 3).

TABLE 4.—Cases with Normal pH Showing Diminished Buffer Values; Sixteen Cases; Twenty-Five Determinations

Case No.	Medical No.	Diagnosis	Blood							Remarks*
			Date	pH	+ N/50 HCl (c.c.)			+ N/50 NaOH (c.c.)		
					0.1	0.2	0.3	0.1	0.2	0.3	
1	5088	Intestinal parasitism; (Balantidium coli); marked anemia	4/22/15	7.45	7.45	7.45	7.45	7.7	7.75	7.75	Alveolar CO_2 tension, 28.6 mm.; blood R. B. C., 1,548,000; Hb., 20 per cent. (Sahli).
2	3408	Bronchopneumonia	4/25/15	7.4	7.3	7.3	7.25	7.45	7.5	7.5	Alveolar CO_2 tension, 16.2 mm.; extreme prostration with mental torpor; uremia suspected; died; necropsy showed no renal lesions.
3	24693	Chronic nephritis; hypertension; albuminuric retinitis	9/10/15	7.45	7.45	7.45	7.45	7.65	7.65	7.65	Blood urea, 102 mg.; phthalein test, 5 per cent. in two hours; Ambard's K., 0.715.
			10/ 7/15	7.55	7.55	7.55	7.55	7.55	7.7	7.75	Blood urea, 78 mg.; Ambard's K., 0.572.
4	34753	Mercuric chlorid poisoning	9/24/15	7.6	7.55	7.55	7.45	7.6	7.65	7.65	Alveolar CO_2 tension September 25, 26.8 mm.; fifth day since taking 7½ grain tablet; anuric since.
			9/27/15	7.55	7.55	7.55	7.55	7.65	7.75	7.75	Eighth day, voided 110 c.c.; anuria for seven days preceding; intensive alkali therapy.
			9/28/15	7.7	7.7	7.65	7.45	7.7	7.75	7.85	Alveolar CO_2 tension, 33 mm.; 485 c.c. urine voided; blood T. N. P. N., 173 mg.
			9/29/15	7.65	7.65	7.65	7.55	7.65	7.75	7.8	Phthalein, 0' Ambard's K., 1.09; 1,185 c.c. urine voided.
			10/ 6/15	7.5	7.5	7.5	7.45	7.6	7.65	7.65	Alveolar CO_2 tension, 30.6 mm.; 1,770 c.c. urine voided; T. N. P. N. blood, 42 mg.; phthalein, 27 per cent. in two hours; Ambard's K., 0.186.
			10/ 8/15	7.55	7.55	7.45	7.45	7.55	7.6	7.65	Alveolar CO_2 tension, 39.1 mm.; 2,120 c.c. urine voided; T. N. P. N. blood, 26 mg.; phthalein, 35 per cent. in two hours; Ambard's K., 0.124; recovered.
5	3085	Diabetes mellitus; chronic nephritis	9/24/15	7.45	7.4	7.35	7.35	7.55	7.55	7.55	Alveolar CO_2 tension September 26, 22.8 mm.; voluntary starvation; much acetone and diacetic acid in urine; getting sod. bicarb., 2 dr. every four hours.
6	34774	Diabetes mellitus (renal)	9/30/15	7.6	7.5	7.5	7.45	7.6	7.6	7.6	Before starvation, blood sugar, 0.13 per cent.
			10/ 4/15	7.45	7.45	7.45	7.45	7.45	7.45	7.45	Starved for past four days; no alkali; Ambard's K., 0.112; blood urea, 29 mg.
			10/ 7/15	7.45	7.45	7.45	7.4	7.45	7.45	7.6	Starved for seven days; no alkali; persistent glucosuria without hyperglycemia; acetone and diacetic acid in urine.
7	34776	Cerebral arteriosclerosis; cerebral hemorrhage	9/30/15	7.45	7.45	7.45	7.45	7.5	7.55	7.55	In coma; marked cyanosis; respiration labored; died same day.
8	34831	Typhoid fever.....	10/14/15	7.5	7.5	7.5	7.45	7.6	7.6	7.6	Temperature at 2 p. m., 103 F.; ice sponge at 2:15; blood drawn at 2:40; patient having chill.
9	34845	Typhoid fever.....	10/14/15	7.45	7.45	7.45	7.45	7.55	7.6	7.65	Temperature at 2 p. m., 103 F.; ice sponge at 2:15; blood drawn at 3.
10	34869	Diabetes mellitus.....	10/26/15	7.55	7.55	7.45	7.45	7.65	7.65	7.65	Acetone and diacetic acid in urine; has been getting 24 gm. sod. bicarb. daily for past six days; alveolar CO_2 tension, 32.1 mm.; blood sugar, 0.138 per cent.
11	34932	Acute tuberculous pneumonia	10/27/15	7.45	7.45	7.45	7.45	7.5	7.65	7.7	Consolidation of entire right lung and part of left lung; respirations labored, rapid and shallow.
12	34944	Bacillary dysentery..	10/28/15	7.55	7.55	7.5	7.45	7.6	7.6	7.65	Prolonged diarrhea; 10 to 12 stools daily for several weeks; marked emaciation and weakness; died.
13	G. U.	Hypertrophy of prostate; operation	11/ 3/15	7.45	7.45	7.45	7.4	7.45	7.55	7.55	Just before operation (control).
				7.4	7.35	7.35	7.3	7.4	7.4	7.4	Immediately after operation; perineal prostatectomy; gas and ether (1 fl. oz.) anesthesia lasting 40 minutes.
14	Obst.	Pregnancy (9th mo.)	11/ 4/15	7.45	7.45	7.45	7.45	7.5	7.55	7.6	
15	Obst.	Pregnancy (9th mo.)	11/ 4/15	7.45	7.45	7.45	7.45	7.55	7.55	7.55	
16	Bay View	Acute yellow atrophy of liver	11/17/15	7.45	7.45	7.45	.....	7.55	7.55	.....	Alveolar CO_2 tension, 34.1 mm. Hg; in coma; died three days later; necropsy.

* The values of Ambard's coefficient, total N. P. N. and urea were determined by the staff of the Chemical Division of the Medical Clinic, to whom we are indebted for the privilege of using them. The nitrogen and urea figures represent mg. per 100 c.c. We desire to thank Dr. J. H. King for a number of alveolar CO_2 determinations.

The values obtained are uniformly slightly lower than those observed in the series of normals, but otherwise present no features of especial interest.

3. *Cases with Normal pH and Diminished Buffer Values.*—(Tables 4 and 5.) An analysis of these tables shows essentially normal buffer and reserve buffer values for acid, markedly diminished values for alkali, and therefore lowered values both for total and total reserve buffers.

Several points of interest are evident from a consideration of this group of cases. It is striking that a diminished buffer for alkali is far more common than that for acid in cases which do not show a *true* acidosis, but in which there is a tendency toward acidosis, as evidenced in many instances by a lowering of the tension of the alveolar carbon

TABLE 5.—CASES WITH NORMAL pH AND DIMINISHED BUFFER VALUES; SIXTEEN CASES; TWENTY-FIVE DETERMINATIONS

		Blood	
		Extremes	Group Average
Buffer	For acid	0 - 0.3	0.19
	For alkali	0 - 0.3	0.09
	Total	0 - 0.6	0.25
Reserve buffer	For acid	0 - 0.3	0.26
	For alkali	0 - 0.3	0.18
	Total	0.3 - 0.6	0.44

dioxid. (Cases 1, 2, 4, 5, 10 and 16.) The diminished buffer for alkali observed in two cases of normal pregnancy (Cases 14 and 15) is in accordance with the almost constant finding of a lowered alveolar carbon dioxid tension during the months of gestation.[11]

Case 4 (mercuric chlorid poisoning) shows at various stages during the clinical course several phases of buffer loss. At first, after five days of anuria, there was loss of buffer for acid; with slight clinical improvement and the reestablishment of urinary secretion, buffer for acid returned, whereas that for alkali was diminished. After intensive alkali therapy, an alkalosis was established though the alveolar carbon dioxid was still somewhat lowered; the buffer values were normal. October 6, a slight set-back occurred, with loss of buffer for alkali. It was prognosticated at this time from the buffer determinations that the alveolar carbon dioxid tension, which two days previously had been normal,

11. Leimdörfer, A., Novak, J., and Porges, O.: Ztsch. f. klin. Med., 1912, lxxv, 301.

TABLE 6.—Acidosis; Nine Cases; Twenty-Four Determinations

Case No.	Medical No.	Diagnosis	Date	Blood						Alveolar CO_2 Tension mm. Hg	Remarks
				pH	+ $\frac{N}{50}$ HCl (c.c.)			+ $\frac{N}{50}$ NaOH (c.c.)			
					0.1	0.2	0.3	0.1	0.2	0.3	
1	32948	Acute and chronic nephritis; hypertension; uremia; albuminuric retinitis	4/20/15	7.35	7.35	7.35	7.3	7.6	7.6	7.65	....	Patient comatose; Ambard's K., 3.3.
			4/21/15	7.4	7.3	7.2	....	7.4	7.45	....	10.4	Died two days later; necropsy.
2	33799	Chronic nephritis; uremia	4/20/15	7.2	7.15	7.15	7.1	7.35	7.45	7.45	....	Ambard's K., 1.99; T. N. P. N. blood, 192 mg.
			4/21/15	7.15	6.9	6.9	....	7.15	7.25	....	11.0	Dull; nausea and vomiting; headache; died four days later; necropsy.
3	34086	Chronic nephritis; hydronephrosis (left); uremia; secondary anemia	4/21/15	7.05	7.0	6.9	....	7.15	7.2	....	0.0	Patient comatose; marked "air hunger"; two hours later, given 500 c.c. blood by syringe transfusion and 400 c.c. 4 per cent. sod. bicarb. intravenously; symptomatically unimproved, but at end of injection, pH of blood = 7.45; died with acute pulmonary edema four hours after the transfusion; Ambard's K. = 3.68 ten hours before death; T. N. P. N. blood, 232 mg.
4	34725	Chronic nephritis; hypertension; uremia; secondary anemia	10/ 4/15	7.55	7.35	7.3	7.15	7.35	7.4	7.45	25.0	T. N. P. N. blood, 181 mg.
			10/ 5/15	7.35	7.25	7.15	7.15	7.35	7.45	7.45	15.7	Venesection for 650 c.c. blood on October 4.
			10/ 7/15	7.35	7.3	7.0	6.9	7.45	7.45	7.55	11.0	Given 300 c.c. 4 per cent. sol. sod. bicarb. + 200 c.c. 5 per cent. glucose sol. intravenously on this day; alveolar CO_2 tension immediately before injection, 11 mm.; immediately after, 17.5 mm.; marked "air hunger"; respirations, 8 per minute; vomiting.
			10/ 8/15	1.35	7.25	7.15	7.15	7.45	7.45	7.45	....	Twenty-four hours later; at this time given 400 c.c. of 4 per cent. sol. sod. bicarb.
				7.55	7.55	7.45	7.35	7.55	7.6	7.7	....	Immediately after injection of the sod. bicarb.; respirations somewhat faster; still in coma.
				7.55	7.45	7.4	7.35	7.55	7.6	7.6	....	One and one half hours after alkali injection; breathing slow and labored; respirations, 8 per minute.

			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Twenty-four hours later marked "air hunger", respirations, 12 per minute; in deep coma; at this time, given 300 c.c. of 4 per cent. sol. sod. bicarb. + 300 c.c. of a phosphate mixture (KH_2PO_4 + Na_2HPO_4) having pH of 7.4
				[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Immediately after the injection; no change in condition; died two hours later; urine alkaline throughout stay in hospital; pH 7.6
[illegible]	[illegible]	[illegible] kink, hydronephrosis, operation	[illegible]	[illegible]	[illegible]	[illegible]	7.1	[illegible]	[illegible]	[illegible]	Just before operation. (Control.) Patient in excellent condition.
				[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.35	7.4	Immediately after operation; cutting of aberrant vessels pressing on ureter; gas anesthesia lasting 1 hour and 35 minutes; uneventful postoperative recovery.
[illegible]	[illegible]	Diabetes mellitus, syphilis, aneurysm of thoracic aorta	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.15	7.2	[illegible]	Comatose; marked "air hunger"; blood sugar, 0.6 per cent
			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.45	[illegible]	[illegible]	Conscious, though mentally dull; during past twenty-four hours received about 1 oz. of sod. bicarb. by mouth, and 500 c.c. of a saturated solution per rectum; died in coma two days later
[illegible]	[illegible]	Acute and chronic hepatitis, [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.35	In coma, having repeated convulsions; phthalein, [illegible] per cent. in two hours
			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Mentally clear; much improved after sweating and bleeding.
[illegible]	[illegible]	Diabetes mellitus, hydronephrosis, chronic morphinism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Drowsy, though mentally clear; respirations [illegible] deep, no "air hunger"; blood urea 16 mg.; phthalein test 42 per cent. in two hours; blood sugar, 0.35 per cent.
			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Alveolar CO_2 November 30 = 55.0 mm.; starved; blood sugar, 0.25 per cent
			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	After intensive intravenous alkali therapy; still mentally dull; getting small amount of broth, green vegetables, and eggs; died two days later
[illegible]	3?04	Carcinoma of stomach; large hepatic metastases, marked secondary anemia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Marked "air hunger"; stuporous. R. B. C., 1,500,000; Hb (Sahli), 23 per cent.; phthalein, [illegible] per cent. in two hours
			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Condition unchanged; died next day; necropsy

would be found to be again lowered, which, indeed, proved to be true. Finally, during convalescence, both pH and buffer values became normal.

The loss of buffer for alkali observed in two instances of febrile typhoid (Cases 8 and 9) is in accord with the tendency toward acidosis which we have observed in several cases of this disease.

TABLE 7.—[illegible] Cases; Twenty-Four Determinations.

		Blood			
		Acid		Total	
	Averages	Extremes	Averages	Extremes	Averages
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE 8.—Summary of Acid, Alkali and Total Buffer Values [illegible] Various Case Groups Expressed as Group Averages.

	Blood		
	Acid	Alk[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
Miscellaneous cases with normal pH [illegible] buffer values	0.4	[illegible]	[illegible]
[illegible] pH [illegible]	0.2	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	0.3	[illegible]	[illegible]

4. *Acidosis.*—(Tables 6 and 7.) From the tables it is evident that cases of acidosis have less buffer for both acid and alkali during the stage of uncompensated acidosis (increased pH of the blood) than during the stage in which the tension of alveolar carbon dioxid is diminished, but the pH of the blood is normal (stage of compensation). Despite the return to normal of pH and buffer values, the clinical evidences of acidosis may persist (Cases 4 and 8).

EXPERIMENTAL CONSIDERATIONS.

Inasmuch as the buffer value of blood is fairly constant in health and decreased in acidosis, the question obviously arises as to whether buffer can be supplied. The possibility of accomplishing this with

phosphate mixtures was considered. The buffer values of phosphate mixtures ($Na_2HPO_4 + KH_2PO_4$) of various strengths and hydrogen-ion concentrations, were therefore determined, the results appearing in Table 9.

From this study four interesting facts are evident: First, the buffer value of blood is greater than that of 1/15 molecular phosphate mixtures and approximately that of 1/5 molecular mixtures; second, the buffer value is greater at neutrality than in more alkaline mixtures; third, the dialysates exhibit buffer values comparable to those obtained by adding the indicator directly to the original mixtures, but [illegible]

TABLE 9. -BUFFER VALUE OF PHOSPHATE MIXTURES ($Na_2HPO_4 + KH_2PO_4$)

	Molecular		1/15 Molecular	1.5 M	
	Undialyzed	Dialysate	Undialyzed	Undialyzed	Dialysate
pH	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0.01	7.4	7.25	7.45	7.4	
0.01	7.3	7.15	7.45	7.4	
[illegible]	7	[illegible]		[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	7	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]		[illegible]	

[illegible] ALL READINGS ON UNDIALYZED MIXTURES

pH	7.05	7.3	7.9	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	

uniformly more acid level; and, finally, the more concentrated the mixture employed, the less marked is the discrepancy between the undialyzed mixture and dialysate.

Attempts to increase the buffer value of the blood by intravenous injection of phosphate mixtures into animals and into a human case (Table 6, Case 4) failed, but demonstrated the following facts:

1. The phosphate mixtures are relatively nontoxic.[12]

12. See also Greenwald, J. Amer. Pharmaceut. Assoc. Pract. Ed., 1915, viii, 57.

TABLE 10.—Protocol of Experiment 1. Injection into a Dog of Third Normal Hydrochloric Acid, Followed by a 4 Per Cent. Solution of Sodium Bicarbonate*

MALE; WEIGHT, 8.6 KG.

Time	Total Amount Injected (c.c.)		Blood							Alveolar CO_2 Tension, mm. Hg	Remarks
				+ N/50 HCl (c.c.)			+ N/50 NaOH (c.c.)				
	N/3 HCl	4% $NaHCO_3$	pH	0.1	0.2	0.3	0.1	0.2	0.3		
12:10	...	...	7.55	7.55	7.45	7.45	7.55	7.55	7.55	38.6	Dog on table; respirations, 28 per min.; pulse, 31 to ¼.
12:25	⟶	..	....	....	....	....	....	....	....	....	Injection of HCl begun.
12:40	75	..	7.35	7.35	7.35	7.3	7.35	7.35	7.35	31.9	
12:46	150	...	....	....	....	....	....	....	....	....	Breathing is slow and deep; salivating profusely; muscles relaxed; defecating involuntarily; seems much distressed; injection stopped.
12:50	...	...	7.15	7.15	7.1	....	7.15	7.2	7.2		
1:00	155	..	....	....	....	....	....	....	....	....	Marked "air hunger"; involuntary defecation continues.
1:05	...	...	....	....	....	....	....	....	....	27.4	Respirations, 16 per min., deep and irregular; pulse, 23 to ¼.
1:07	165 ⟵	...	....	....	....	....	....	....	....	....	The injection of the last 10 c.c. of acid immediately caused deepening and quickening of respiration.
1:08	...	⟶	....	....	....	....	....	....	....	....	Injection of $NaHCO_3$ begun.
1:14	...	85	....	....	....	....	....	....	....	....	Respirations decidedly shallower; animal still relaxed and quiet.
1:20	..	...	7.35	7.35	7.3	7.2	7.4	7.45	7.45		
1:25	...	120	....	....	....	....	....	....	....	39.5	
1:35	..	250	7.6	7.6	7.5	...	7.6	7.6	7.6	43.8	Animal more animated; struggling.
1:49	..	350	....	....	....	....	....	....	....	....	Free diuresis; pH of urine, 7.65.
1:59	...	500	....	....	....	....	....	....	....	....	Injection stopped.
2:05	...	...	7.7	7.7	7.6	7.6	7.7	7.8	7.8	48.0	
2:12	...	...	....	....	....	....	....	....	....	....	Animal seems weak; breathing quietly; sacrificed.

* Injections made into leg vein; blood for examination withdrawn from jugulars; N/3 HCl made up in 0.8 per cent. salt solution; bicarbonate solution made up in distilled water. Arrows mark beginning and end of injections.

TABLE II.—Protocol of Experiment 2. Injection into a Dog of a 4 Per Cent. Solution of Sodium Bicarbonate, Followed by N/3 Hydrochloric Acid.* Male; Weight, 6.25 kg.

Time	Total Amount Injected (c.c.)		Blood							Alveolar CO_2 Tension, mm. Hg	Remarks
				+ $\frac{N}{50}$ HCl (c.c.)			+ $\frac{N}{50}$ NaOH (c.c.)				
	4% $NaHCO_3$	N/3 HCl	pH	0.1	0.2	0.3	0.1	0.2	0.3		
10:50	...	...	7.35	7.35	7.3	7.2	7.35	7.4	7.45	41.4	Dog on table.
10:53	→	...	....	....	....	....	....	....	....	....	Injection of alkali begun.
11:15	175	...	....	....	....	....	....	....	....	....	Animal very restless.
11:20	200	...	7.8	7.7	7.7	....	7.8	7.85	....	53.7	Injection stopped.
11:30	...	...	....	....	....	....	....	....	....	....	Injection resumed; quieter.
11:35	275	...	....	....	....	....	....	....	....	....	Deep, snorting respirations; watery defecation.
11:38	355 ←	...	....	....	....	....	....	....	....	....	Still defecating at intervals; profuse diuresis; pH urine, 7.55; injection of alkali stopped.
11:50	...	...	7.75	7.7	7.65	7.6	7.75	7.9	7.9	63.7	
12:11	...	→	....	....	....	....	....	....	....	....	Injection of acid begun.
12:16	...	50	....	....	....	....	....	....	....	....	Restless.
12:20	...	...	....	....	....	....	....	....	....	....	Respirations 20 per minute, slow, deep and regular.
12:24	...	150	7.37	7.35	7.2	7.15	7.4	7.4	7.5	40.1	
12:38	...	200	....	....	....	....	....	....	....	....	Respirations very slow and deep.
12:42	...	250 ←	7.3	7.2	7.15	....	7.3	7.35	7.35	27.9	
1:00	...	...	....	....	....	....	....	....	....	....	Dog seems in fairly good condition. Still passing watery stools. Recovered.

* Injections made into leg vein; blood for examination withdrawn from jugulars; solution of bicarbonate made up in distilled water; HCl made up in 0.8 per cent. salt solution. Arrows mark beginning and end of injections.

2. The injection of sodium phosphate (Na_2HPO_4) (800 c.c. of a $\frac{1}{5}$ molecular solution representing 28.5 gm. of the salt) into an animal of 11 kg. did not produce an alkalosis or increase the buffer values, whereas the injection of 750 c.c. of a $\frac{1}{15}$ molecular mixture of di-sodium phosphate (Na_2HPO_4) and acid potassium phosphate (KH_2PO_4) at pH 7.0 into a dog weighing 6.65 kg., produced a mild acidosis without appreciable change in buffer values.

3. The intravenous injection of 300 c.c. of a phosphate mixture at pH 7.4, together with 300 c.c. of a 4 per cent. solution of sodium bicarbonate in the case of a man dying in uremic coma, caused a change in the pH of the blood from 7.35 to 7.55, and increased the buffer for alkali but not for acid. There was no change in the clinical condition of the patient, who died two hours later.

Buffer Values in Experimental Acidosis and Alkalosis.—(Tables 10 and 11). It is seen from Experiment 1 that in the acidosis produced by the intravenous injection of an inorganic acid (hydrochloric acid) the buffer values may remain practically normal, although there is a decided lowering of the alveolar carbon dioxid and a marked increase in the pH of the blood. This is in accord with what is sometimes found in the acidosis of chronic nephritis with uremia and in that of diabetes (Table 6, Cases 4 to 9, inclusive). After injection of alkali to overcome the acidosis, there is a transient diminution in the buffer for alkali, followed by a prompt return to normal values as the pH of the blood is lowered.

In experimental alkalosis the buffer for acid is first diminished. The alveolar carbon dioxid rises to unusually high figures—63.7 mm. in this animal. After injection of sufficient hydrochloric acid to overcome the alkalosis and produce a mild acidosis with lowered alveolar carbon dioxid tension, the buffer for both acid and alkali is lowered.

In the instance of mercuric chlorid poisoning (Case 4, Table 4), in which the patient received large doses of sodium bicarbonate both by mouth and intravenously, a similar condition of alkalosis was produced, though here the buffer values remained normal at this stage of the disease, and the alveolar carbon dioxid tension was still low—33.0 mm. of mercury.

SUMMARY

1. A simple method is described for determining quantitatively the buffer value of the blood. It consists in adding increasing amounts of fiftieth-normal hydrochloric acid and fiftieth-normal sodium hydroxid solution to equal quantities of blood and observing the resulting changes in hydrogen-ion concentration by means of the dialysis-indicator method.

2. The results are expressed in terms of cubic centimeters of fiftieth normal acid or alkali per 2 c.c. of blood.

3. The buffer values of blood for acid and alkali yield valuable information from a clinical standpoint. The reserve and total buffers may also be calculated from the results of the determinations.

4. The minimal values for normal blood have been determined; considerably larger values may be encountered. For a group of miscellaneous cases with normal pH, the average buffer values were somewhat lower, though within normal limits.

5. In certain cases with normal pH of the blood, but showing a tendency toward the development of an acidosis (as evidenced, for example, by lowered alveolar carbon dioxid tension), the buffer values were diminished. The loss of buffer for alkali was far more striking and frequent than for acid, and was often associated with lowered alveolar carbon dioxid tension. As a result of therapy, especially the use of alkali, the buffer values in some instances returned to normal.

6. In a series of cases of acidosis the average buffer values were found to be markedly diminished, particularly during the stage in which the pH of the blood was abnormally high. Normal buffer values may be encountered, however, in the presence of a true acidosis. Coincident with clinical improvement following treatment, particularly intensive alkali therapy, both pH and buffer values approximated or became normal in several cases.

7. It was not possible to supply buffer to the blood by the injection of phosphate mixtures.

8. By the intravenous injection of third-normal hydrochloric acid and 4 per cent. sodium bicarbonate solution into dogs, conditions of acidosis and alkalosis were produced which were inconstantly accompanied by changes in the buffer values of the blood.

9. The determination of the buffer value of the blood, especially in cases in which an acidosis is suspected or present, yields information of some diagnostic and prognostic significance and permits of a more complete study of the factors concerned in the maintenance of the acid-base equilibrium of the body.